Cerebral $GABA_A$ and $GABA_B$ Receptors

Structure and Function

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γ-Aminobutyric acid (GABA) is widely known as one of the major inhibitory neurotransmitters in the mammalian central nervous system (CNS).[1] In general, it has been considered that neuronal activity in the brain is inhibited by the activation of GABAergic neurons. This inhibitory action of GABA is mediated by GABA receptors, which are divided into two types—$GABA_A$ and $GABA_B$.[2] It was initially thought that $GABA_A$ receptor, a bicuculline-sensitive type, forms the GABA-gated Cl^- channel, and that the activation of $GABA_A$ receptor induces the fast inhibitory postsynaptic potential (IPSP). Subsequently, the presence of $GABA_B$ receptor, which is insensitive to bicuculline and sensitive to baclofen, was revealed, and it was found that this receptor is one of the metabotropic types that couple with GTP-binding protein. The activation of the $GABA_B$ receptor is known to induce slow IPSP. Therefore, it is suggested that both $GABA_A$ and $GABA_B$ receptors have inhibitory roles in the CNS, although these actions are mediated by different molecular mechanisms.

In this paper, current concepts on $GABA_A$ and $GABA_B$ receptors in the mammalian CNS are described, with special reference to their pharmacological, neurochemical, and molecular biological characteristics.

$GABA_A$ RECEPTOR

Pharmacology of $GABA_A$ Receptor

The application of GABA induces the increase of Cl^- conductance at GABAergic synapses. This increase is antagonized by bicuculline, a $GABA_A$ receptor antagonist. Picrotoxin, which induces tonic-clonic convulsions, and convulsant compounds such as *t*-butylbicyclophosphorothionate (TBPS) also bind to the Cl^- channel in the $GABA_A$ receptor complex and depress Cl^- conductance, although these compounds have no action on the GABA binding (recognition) site. Barbiturate derivatives, which are classified as one of the sedative hypnotic drugs, are also known to enhance the action of GABA by affecting the Cl^- channel site of the $GABA_A$

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receptor complex. On the other hand, anxiolytic and/or hypnotic drugs such as benzodiazepine derivatives are known to activate the GABA binding site in the $GABA_A$ receptor complex. It is noteworthy that the binding site for benzodiazepines, which is coupled with the $GABA_A$ receptor and the Cl^- channel, has been termed benzodiazepine receptor. Benzodiazepine receptor agonists such as diazepam and flunitrazepam, as well as benzodiazepine antagonists such as flumazenil, bind to the benzodiazepine receptor. In contrast, β-carboline derivatives are known to induce anxiety by an inhibitory modulation of $GABA_A$ receptor function through the benzodiazepine receptor. Therefore, these compounds are often termed as inverse agonist of benzodiazepine receptor. It has been also noted that various drugs and endogenous products in the brain affect the function of $GABA_A$ receptor/benzodiazepine receptor/Cl^- channel complex.[3] For example, it has been reported that neurosteroids such as 3α-hydroxy-5α-dihydroprogesterone also bind to the Cl^- channel site in the $GABA_A$ receptor complex and act as putative endogenous modulators for stress and anxiety.[4,5] These characteristics of the $GABA_A$ receptor have been recognized using various pharmacological and electrophysiological approaches. Furthermore, purification and reconstitution studies on the $GABA_A$ receptor complex have provided direct evidence for these pharmacological characteristics.

Purification and Characterization of $GABA_A$ Receptor Complex

Functional as well as structural coupling of the $GABA_A$ receptor with the benzodiazepine receptor was found to be useful for the purification of the $GABA_A$ receptor complex in the CNS. We previously purified the $GABA_A$ receptor complex by means of affinity column chromatography using a benzodiazepine, 1012-S, as an immobilized ligand.[6] The purified protein of the $GABA_A$ receptor complex from rat brain had the molecular weight of approximately 300,000 and consisted of α (48,500) and β (54,500) subunits. Similarly, $GABA_A$ receptor from the bovine cerebral cortex was found to consist of α (53,000) and β (57,000) subunits.[7] These purified receptor preparations were shown to retain functional coupling between $GABA_A$ and benzodiazepine receptors even after the purification. Namely, [^{3}H]muscimol binding to the $GABA_A$ receptor was enhanced by benzodiazepine receptor agonists, whereas the enhancement was inhibited by flumazenil, an antagonist of the benzodiazepine receptor. Similarly, $GABA_A$ receptor agonists enhanced [^{3}H]flunitrazepam binding to the benzodiazepine receptor, whereas the enhancement was inhibited by bicuculline, a $GABA_A$ receptor antagonist. It was also shown that when the purified $GABA_A$ receptor complex is reconstituted into the phospholipid vesicles, the application of GABA to the reconstituted vesicles induces an increase in the $^{36}Cl^-$ influx, whereas flunitrazepam, a benzodiazepine receptor agonist, potentiates the GABA-stimulated $^{36}Cl^-$ influx.[8] These experimental results have provided evidence that the $GABA_A$ receptor couples with the benzodiazepine receptor and forms the GABA-gated Cl^- channel.

Distribution of $GABA_A$ Receptor Complex in the Central Nervous System

The specific antibody against purified $GABA_A$ receptor complex was prepared by the immunization of albino rabbits with the purified protein.[9] The distribution of the $GABA_A$ receptor complex in rat brain was examined immunohistochemically using this specific antibody. Immunoreaction in rat brain slices was recognized in various

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regions of the CNS such as the ventromedial nucleus of the hypothalamus, the red nucleus, the globus pallidus, the zona compacta and zona reticulata of the substantia nigra, the layers of Purkinje cells and granular cells in the cerebellum, layers III–V of cerebral cortex, and the stratum radiatum of the hippocampus. These immunoreactive regions coincided well with the results of immunohistochemical studies using antibody against L-glutamic acid decarboxylase, the enzyme for the synthesis of GABA.

Structure of $GABA_A$ Receptor Complex

The structural analysis of the $GABA_A$ receptor complex was advanced rapidly by the application of cDNA cloning. The cDNAs of $GABA_A$ receptor α and β subunits from bovine brain were cloned.[10] Subsequently, cDNA cloning of many subunits of the $GABA_A$ receptor complex was achieved by the application of homologous screening. The presence of α, β, γ, δ, and ρ subunits in the brain was reported, respectively.[10–15] Moreover, the heterogeneity of $GABA_A$ receptor subunits was found as shown in TABLE 1. In brief, the $GABA_A$ receptor complex consists of a combination of four or five subunits, where various combinations of these subunits result in the heterogeneity of $GABA_A$ receptor molecules.[16,17] In fact, the pharmacological properties of recombinant $GABA_A$/benzodiazepine receptor complex were

TABLE 1. Multiplicity of $GABA_A$ Receptor Subunits

α_1, α_2, α_3, α_4, α_5, α_6
β_1, β_2, β_3, β_4, $\beta_{4'}$
γ_1, γ_{2S}, γ_{2L}, γ_3, γ_4
δ
ρ_1, ρ_2

NOTE: β_4 and $\beta_{4'}$, γ_{2S} and γ_{2L} are derived from the alternative splicing, respectively.

found to be different by the use of different combinations of various subunits.[12,13,18,19] The results from cDNA cloning of the $GABA_A$ receptor complex indicated the existence of a high homology among the various subunits examined. Notably, four regions of high hydrophobicity in the structure were conserved and suggested the presence of four transmembrane (TM) domains. The structure of $GABA_A$ receptor subunits was also found to be homologous among different species. These characteristics were similar to those in other ionotropic receptors. Therefore, it was assumed that the ligand-gated ion channels constituting the $GABA_A$ receptor complex are members of a superfamily.[20] Furthermore, it was suggested that the TM II domain has an important role in the formation of the ion channel pore. It has been found that in anion channels, the common sequence, TTVLTMTTXS, in the TM II domain of both $GABA_A$ and glycine receptor subunits is hydroxy-rich, and that this sequence is not conserved as in the case of cation channels such as the nicotinic acetylcholine receptor. Consequently, it has been presumed that this region is important for the recognition of the Cl^- ion. Furthermore, it has been reported that the mutations in the channel domain of a neuronal nicotinic receptor convert ion selectively from cationic to anionic.[21] These results indicate that the structure of membrane domains is important for maintaining the selectivity of ions.

In the intracellular loop of TM III–IV in each subunit, the presence of putative sites of phosphorylation by cAMP-dependent protein kinase and/or protein kinase C

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was noted. In fact, it was reported that these protein kinases phosphorylate the purified $GABA_A$ receptor protein.[22,23] Furthermore, it was demonstrated that the phosphorylation of the $GABA_A$ receptor modulates the function of the $GABA_A$ receptor complex.[24]

Expression of mRNA for $GABA_A$ Receptor Complex

It is well known that the function of the $GABA_A$ receptor is modulated by treatment with various drugs. A good example for this is down-regulation of the receptor following continuous agonist stimulation. In fact, treatment of primary cultured cerebral cortical neurons with muscimol, a selective $GABA_A$ receptor agonist, induced the reduction of expression of $GABA_A$ receptor α_1-subunit mRNA.[25] This reduction was counteracted by simultaneous treatment with bicuculline, a $GABA_A$ receptor antagonist. Moreover, the treatment with flunitrazepam, an agonist of the benzodiazepine receptor, which coupled with the $GABA_A$ receptor, also caused a decline of the expression of mRNA for $GABA_A$ receptor α1-subunit, and this change was also counteracted by simultaneous treatment with flumazenil, an antagonist of the central type of benzodiazepine receptor. These results suggest that continuous stimulation of the $GABA_A$ receptor complex by its agonists may induce the reduced expression of mRNA for the $GABA_A$ receptor subunits. By contrast, the treatment with inverse agonist for the benzodiazepine receptor such as β-carboline derivatives induced an increase of $GABA_A$ receptor subunit mRNAs.[26] Therefore, it is suggested that the expression of mRNA for $GABA_A$ receptor subunits may be regulated by positive and/or negative signal transductions through the $GABA_A$ receptor complex.

Recently, it has also been reported that the expression of mRNA for $GABA_A$ receptor subunits is modulated by activation of the *N*-methyl-D-aspartate-sensitive glutamate receptor.[27] Therefore, it is likely that the transcriptional mechanism for $GABA_A$ receptor subunit genes may be regulated by not only the direct stimulation or inhibition of the $GABA_A$ receptor complex, but also the functional state of neuronal networks connected to GABAergic neurons.

$GABA_B$ RECEPTOR

Pharmacology of $GABA_B$ Receptor

It has been reported that (−)baclofen decreases neurotransmitter releases in the CNS.[28] In 1981, it was established that this effect of (−)baclofen is exerted by the activation of a bicuculline-insensitive and non-$GABA_A$ receptor,[29] and this receptor is termed the $GABA_B$ receptor. Although GABA and (−)baclofen have been used as $GABA_B$ receptor agonists, studies on the physiological and pharmacological roles of the $GABA_B$ receptor in the CNS have been delayed, mainly due to lack of selective and potent antagonists for this receptor. Recently, however, selective and potent agonists and antagonists for the $GABA_B$ receptor have been introduced. For example, 3-aminopropylphosphonous acid (APPA) has been developed as a potent agonist at peripheral and central presynaptic $GABA_B$ receptors.[30] On the other hand, phaclofen and 2-hydroxy saclofen have been introduced as selective antagonists for the $GABA_B$ receptor.[31,32] More recently, it has been reported that CGP35348, having high affinity and high penetrability to the brain, is a potent blocker of the

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$GABA_B$ receptor.[33] Inasmuch as the development of various $GABA_B$ receptor antagonists is under way with high hopes of their clinical applications,[34] it may be possible to obtain more potent and selective $GABA_B$ receptor antagonists in the near future.

The binding of $GABA_B$ receptor was found to be inhibited by the presence of GTP analogues, which induced a decrease in the affinity of the $GABA_B$ receptor.[35,36] In addition, it was reported that stimulation of the $GABA_B$ receptor accentuated the GTPase activity in the crude synaptic membrane.[37] This increase of GTPase activity was hindered by the pretreatment with the islet-activating protein (IAP). These results suggest that $GABA_B$ receptor may be coupled with a GTP-binding protein, such as G_i or G_o, which is sensitive to the IAP treatment.

Activation of the cerebral $GABA_B$ receptor induced the inhibition of cAMP formation.[38,39] The increased formation of cAMP induced by the stimulation of other neurotransmitter receptors and by forskolin was also inhibited by activation of the $GABA_B$ receptor, whereas the pretreatment with IAP abolished the inhibitory action of $GABA_B$ receptor agonists.[40] Therefore, it is thought that stimulation of the $GABA_B$ receptor inhibits the adenylyl cyclase activity via IAP-sensitive GTP-binding protein.

On the other hand, it was reported that activation of the $GABA_B$ receptor resulted in the potentiation of β-adrenergic receptor-mediated cAMP formation.[41] This potentiation was also inhibited by the treatment with IAP.[42] Because the stimulation of the $GABA_B$ receptor induced an increase of binding affinity at the β-adrenergic receptor,[43] a cross-regulation of intracellular signal transduction systems, which were coupled with the β-adrenergic receptor and the $GABA_B$ receptor, was suggested. Detailed mechanisms underlying such cross talk between these two receptors, however, are presently unknown.

It is well known that several neurotransmitter receptors are positively coupled with phosphatidylinositol (PI) turnover, which generates both 1,2-diacylglycerol and inositol-1,4,5-triphosphate. Inositol phosphates formation was also inhibited by the activation of the $GABA_B$ receptor.[44,45] This $GABA_B$ receptor-mediated inhibition of PI turnover was eliminated again by the treatment with IAP.[46] Therefore, it has been suggested that the $GABA_B$ receptor is also negatively coupled with PI turnover, mediated by an IAP-sensitive GTP-binding protein. It is unclear, however, whether the same $GABA_B$ receptor inhibits both adenylyl cyclase and PI turnover systems or different types of the $GABA_B$ receptor (subclasses) are responsible for the inhibition of these intracellular signal transduction systems.

In electrophysiological studies, it was also demonstrated that the activation of the $GABA_B$ receptor resulted in the modulation of ion channels. Namely, a voltage-dependent Ca^{2+} channel was inhibited by the activation of the $GABA_B$ receptor.[47] In addition, the activation of the $GABA_B$ receptor induced an increase in K^+ conductance, which resulted in the occurrence of slow IPSP.[48,49] Modulation of these ion channels by the $GABA_B$ receptor was also known to be mediated by the GTP-binding protein, which is sensitive to IAP treatment. Therefore, it seems likely that the suppression of transmitter release by the activation of the presynaptic $GABA_B$ receptor is caused by a decrease in Ca^{2+} conductance and/or an increase in K^+ conductance.

Neurochemical Aspects of $GABA_B$ Receptor

In neurochemical approaches, the isolation of the $GABA_B$ receptor protein is important to clarify its biochemical properties. For these purposes, solubilization of

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the $GABA_B$ receptor from crude synaptic membranes was attempted, at first using various detergents such as CHAPS.[50] Ligand-affinity column chromatography for the purification of the $GABA_B$ receptor was then attempted using baclofen, a selective agonist for $GABA_B$ receptor, as the immobilized ligand. We developed the baclofen-epoxy-activated Sepharose 6B for this purpose.[50] Using this affinity column, we achieved approximately 11,000-fold purification of the $GABA_B$ receptor. Due to a low affinity of this baclofen-affinity gel, we faced technical difficulties for further

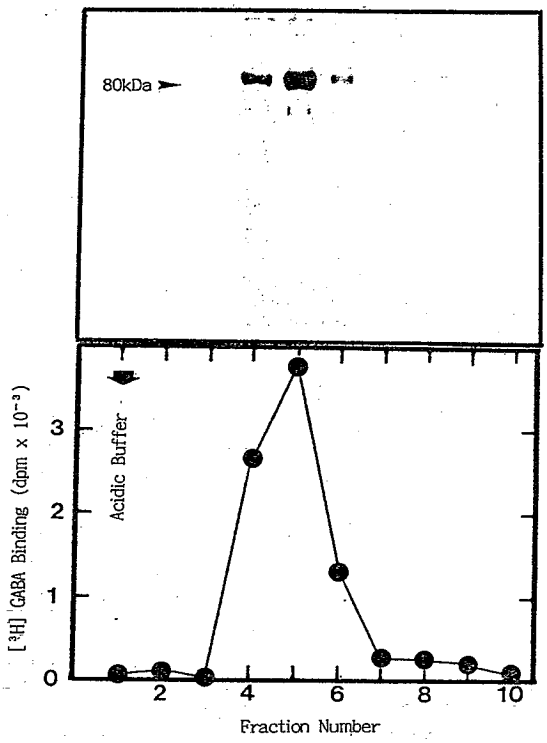

FIGURE 1. Immunoaffinity purification of 80-kDa GABA-binding protein. Solubilized synaptic membrane was incubated with monoclonal antibody-conjugated immunoaffinity beads. Elution was performed by the addition of the acidic buffer (50 mM citrate, pH 2.5) containing 5 mM CHAPS and the protease inhibitors. Eluted fractions were analyzed by SDS-PAGE (*upper panel*) and by [^{3}H]GABA-binding assay (*lower panel*). The SDS-PAGE analysis shows that the major protein band is 80 kDa. Occasionally, one or two faintly stained bands are visible having 65 or 61 kDa (an example of 65 kDa is seen in fraction 5). For the [^{3}H]GABA-binding assay, [^{3}H]GABA (12.5 nM) and purified 80-kDa GABA-binding protein were incubated for 1 h in ice-cold 50 mM Tris-HCl buffer (pH 7.4) containing 2 mM $MgCl_2$, 2 mM $CaCl_2$ in the presence of a soybean phospholipid (final 4 mM). The soybean phospholipid was added to minimize an inhibitory effect of CHAPS (which was contained in the immunoaffinity elute, final 0.5 mM) on the [^{3}H]GABA binding assay. A clear mixture (0.35 mL) became turbid with the addition of the phospholipid. Nonspecific immunoglobulin (2 mg/mL) was also added for complete sedimentation of GABA-binding proteins. Radioactivity bound to these proteins was precipitated by the addition of 0.15 mL of 50% polyethylene glycol and separated from the unbound radioactivity by filtration.

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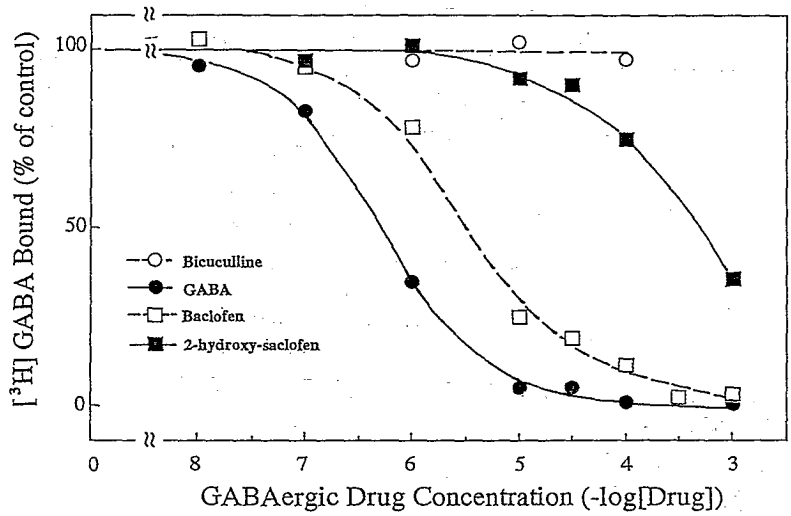

FIGURE 2. Displacement by various GABAergic drugs of [^{3}H]GABA binding to the purified 80-kDa GABA-binding protein. GABAergic drugs at various concentrations were added to the mixture of [^{3}H]GABA-binding assay. Both $GABA_B$ agonist and antagonist apparently bind to GABA-binding protein, whereas $GABA_A$ antagonist bicuculline does not.

purification using this affinity column chromatographic procedure.[51] Therefore, we decided to develop immunoaffinity chromatographic procedures using monoclonal antibody specific to the receptor.

For the production of a monoclonal antibody specific to the $GABA_B$ receptor, the receptor protein from the bovine brain was partially purified using the above-mentioned baclofen-affinity column, and this preparation was injected into mice as an antigen. Spleen cells from mice having high titers of antisera were used for cell fusion. Positive clones were selected by Western blot analysis using the partially purified $GABA_B$ receptor preparation, and a monoclonal antibody (GB-1) for the $GABA_B$ receptor was obtained.[52] In Western blot analysis using the crude synaptic membrane preparation from the bovine brain, the antibody recognized only one protein band among over one hundred protein moieties. The molecular weight of the immunopositive protein was about 80 kDa. It was found that the baclofen-sensitive GABA binding activity to crude synaptic membrane was significantly reduced by the addition of this monoclonal antibody.[52] Furthermore, $GABA_B$ receptor binding activity in the solubilized fraction obtained from bovine synaptic membrane was completely eliminated by immunoabsorbent agarose beads that were conjugated with the antibody. It was also noted that the 80 k-Da protein was immunoprecipitated without visible changes in electrophoresed profiles of total proteins on Western blot analysis.

In order to determine whether or not this GABA-binding protein is truly the $GABA_B$ receptor, the purification of the antigen by an immunoaffinity method was attempted.[53] The 80-kDa GABA binding protein in the solubilized fraction was adsorbed on the immunobeads and eluted with an acidic buffer (pH 2.5). The eluted fraction having the GABA binding activity showed only one protein band (80 kDa) in

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SDS-PAGE (FIG. 1). This binding activity to the purified protein was selectively displaced by GABA, baclofen, and 2-hydroxy saclofen, but not by bicuculline (FIG. 2).

Furthermore, an attempt was made to examine whether or not this 80-kDa GABA binding protein could function as $GABA_B$ receptor using a reconstituted system. Namely, the 80-kDa protein was reconstituted into phospholipid vesicles with partially purified GTP-binding protein (which had G_i and/or G_o, but not G_s) and adenylyl cyclase. The forskolin-stimulated adenylyl cyclase activity was inhibited by the addition of GABA or baclofen to the complete system, whereas such an effect of the $GABA_B$ receptor agonist was not detected in the system that had no 80-kDa protein, adenylyl cyclase or GTP-binding protein. This inhibition by GABA or baclofen was abolished by the simultaneous addition of 2-hydroxy saclofen (FIG. 3). Therefore, it was suggested that the stimulation of 80-kDa GABA binding protein is transduced to adenylyl cyclase via inhibitory GTP-binding protein such as G_i or G_o. These results are also strong evidence supporting the notion that the immunoaffinity-purified 80-kDa protein is indeed the $GABA_B$ receptor.

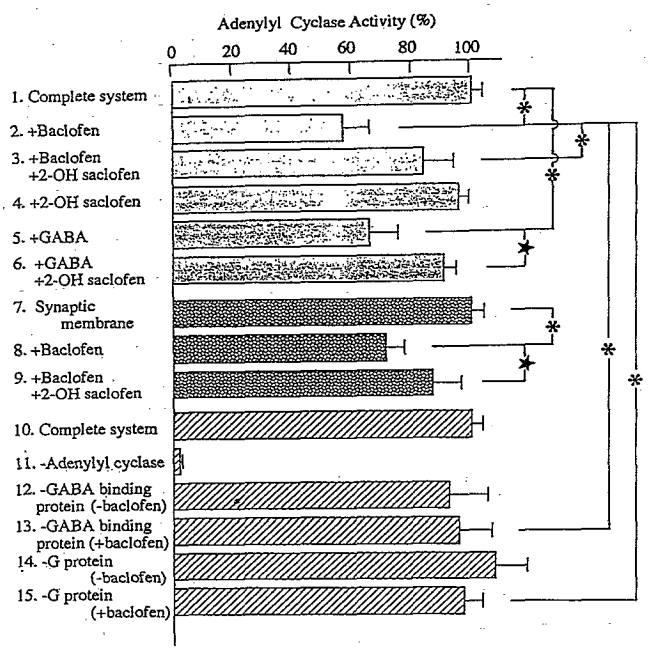

FIGURE 3. Adenylyl cyclase activity on reconstituted membrane (lanes 1–6), synaptic membrane (lanes 7–9), and incomplete reconstituted membrane (lanes 10–15). The incomplete reconstituted membrane preparations are devoid of both adenylyl cyclase (lane 11) and 80-kDa GABA-binding protein (lanes 14 and 15). Forskolin (10^{-5} M) stimulated adenylyl cyclase activity on these membranes was assayed after preincubation of the membrane with or without $GABA_B$ receptor agonist (2×10^{-5} M GABA or 2×10^{-4} M baclofen) or $GABA_B$ receptor antagonist (10^{-3} M 2-hydroxy saclofen).

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CONCLUSION AND FUTURE PROSPECTS

There are two different subtypes of GABA receptors: ionotropic $GABA_A$ and metabotropic $GABA_B$. The $GABA_A$ receptor consists of a receptor complex with the Cl^- channel and the benzodiazepine receptor, whereas the $GABA_B$ receptor negatively couples with adenylyl cyclase and inositol phosphate generating system and also several calcium channels via IAP-sensitive G_i- or G_o-type GTP binding protein.[54–58] The $GABA_A$ receptor complex consists of various subunits and each subunit possesses four transmembrane domains which possibly constitute Cl^- channel. In the case of the $GABA_B$ receptor, it is highly likely that the 80-kDa protein, which we purified using an immunoaffinity column chromatographic procedure, is indeed the $GABA_B$ receptor protein. The primary structure of the $GABA_B$ receptor, however, has not been determined in detail. Molecular cloning of the $GABA_B$ receptor is under way in our laboratory. The locations of $GABA_A$ and $GABA_B$ receptors at synapses also remain to be clarified, as well as the nature of the subtype acting as presynaptic autoreceptor or heteroreceptor in the neuronal network. For these purposes, electron microscopic immunocytochemistry using monoclonal antibodies for $GABA_A$ and $GABA_B$ receptors, mentioned in this study, may be useful in future studies.

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